AMENDMENTS TO THE SPECIFICATION

Please replace the originally submitted Sequence Listing with the Substitute Sequence Listing submitted concurrently herewith.

Please amend the paragraph beginning on page 1, line 35 and continuing onto page 2 with the following amended paragraph:

--A common theme in all of these proteins are the presence of a leucine-repeat repeat (LLR) in the carboxy terminus of the polypeptide chain. LLRs are short protein modules characterized by a periodic distribution of hydrophobic amino acids, especially leucine residues separated by hydrophilic residues [Sean, 1996]. The basic structure of the repeat is as follows:

X-**L**-X-X-**L**-X-**L**-X-X-**N**-X-**a**-X-X-X-**a**-X-X-**L**-X (SEQ ID NO:42)

where X is any amino acid, L is leucine, N is asparagine and "a" denotes an aliphatic residue. The asparagine at position 10 can be replaced by cysteine, threonine or glutamine. The average repeat length is 24 amino acids but it can vary between 22 to 29 amino acids, though some LRR motifs have been reported to be at short as 20 amino acids. The motif often consists of leucine or other aliphatic residues at positions 2, 5, 7, 12, 16, 21, and 24 and asparagine, cysteine or threonine at position 10. X-ray structure determination of LRR motifs suggests that each LRR is composed of a beta-sheet and an alpha-helix. The largest subfamily of proteins that contain a leucine-rich domain are extracellular proteins having the following motif : LxxLxxLxLxxNxLxxLPxxOFxx (SEQ ID NO:43), where"x"is any amino acid and "O"is a non-polar residue (Kajava, J. Mol. Biol. 277: 519 (1998)).--

Please amend the paragraph beginning on page 41, line 32 continuing onto page 42 with the following amended paragraph:

-- Specifically, the HLRRSI1 polypeptide was predicted to comprise one tyrosine phosphorylation site using the Motif algorithm (Genetics Computer Group, Inc.). Such sites are phosphorylated at the tyrosine amino acid residue. The consensus pattern for tyrosine phosphorylation sites are as follows: [RK]-x(2)-[DE]-x(3)-Y SEQ ID NO:44, or [RK]-x(3)-[DE]-x(2)-Y SEQ ID NO:45, where Y represents the phosphorylation site and 'x' represents an intervening amino acid residue. Additional information specific to tyrosine phosphorylation sites can be found in Patschinsky T., Hunter T., Esch F.S., Cooper J.A., Sefton B.M., Proc. Natl. Acad. Sci.

U.S.A. 79:973-977(1982); Hunter T., J. Biol. Chem... 257:4843-4848(1982), and Cooper J.A., Esch F.S., Taylor S.S., Hunter T., J. Biol. Chem... 259:7835-7841(1984), which are hereby incorporated herein by reference.--

Please replace Example 1 on page 200 and continuing onto page 201, with the following amended Example 1:

-- Example 1 – Bioinformatics Analysis.

A Leucine-rich repeat (LLR) domain containing protein, annotated as Angiotensin/Vasopressin receptor AII/AVP (Genbank Accession: AAC39910; SEQ ID NO:25) and other LLR-domain containing proteins such as KIAA0926 (Genbank Accession: NP_055737; SEQ ID NO:26) were used as probes to search the EST databases from Incyte and the public domain, in addition to the genomic database from the Human Genome Project. The search program used was BLAST (Basic Local Alignment Search Tool). From this analysis, ESTs and exons encoding potential novel candidates, related to Angiotensin/Vasopressin receptor, were identified based on sequence homology. The potential candidates (Incyte ESTs: 1632960H1 and Public domain EST GI number: g201045) were sequenced. Two clones were identified, entitled SILRR1A (SEQ ID NO:5; ATCC Deposit No. PTA-2679) and SILRR1B (SEQ ID NO:6; ATCC Deposit No. PTA-2674) was obtained using the EST sequence information.. The sequence of these two clones was combined through contig analysis procedures known in the art to obtain the full-length clone encoding the novel HLRRSI-1 protein. The complete protein sequences of these proteins were analyzed for potential transmembrane domains. TMPRED program (5) was used for transmembrane prediction. Also, these proteins were analyzed for potential motifs and protein domains. Motifs program in GCG (GCG is a software package from Genetics Computer Group of Wisconsin) was used for identifying the potential motifs in the protein. Protein domains were analyzed by using HMMER. HMMER is a freely distributable implementation of profile Hidden Markov Model (HMM) software for protein sequence analysis ~~(http://hmmer.wustl.edu/)~~. The protein domain search set used was Pfam ~~(http://pfam.wustl.edu/)~~. Pfam is a large collection of multiple sequence alignments and hidden Markov models of protein domains covering 2478 protein families. By these analyses, the HLRRSI1 protein has been predicted to comprise one or more leucine-rich repeat domains. --

Please amend the paragraph beginning on page 1, line 23 with the following amended paragraph:

--Recently, a class of cell surface proteins have been described in both plants and animals that are involved in pathogen perception, MHC class II trans-activation , inflammation and the regulation of apoptosis (Inohara, N., Nunez, G, Cell, Death, Differ., 6(9):823-4, (1999); Inohara, N., Koseki, T., del, Peso, L., Hu, Y., Yee, C., Chen, S., Carrio, R.,Merino, J., Liu, D., Ni, J., Nunez, G, J. Biol, Chem. 21., 274(21):14560-7, (1999); Inohara, N., Nunez, G, Cell, Death, Differ., 7(5):509-10, (2000); Harton, JA., Ting, JP, Mol, Cell, Biol., 20(17):6185-94, (2000); Dixon, J., Brakebusch, C., Fassler, R., Dixon, MJ. Hum, Mol, Genet. 12., 9(10):1473-80, (2000)). All of these proteins are modular in nature containing one or several domains that function in caspase ~~recuritment~~recruitment (CARD), nucleotide binding and protein-protein interactions. Proteins within this group have also been found to play a role in cell adhesion during various developmental processes.--

Please amend the paragraph beginning on page 3, line 7, with the following amended paragraph:

--*Slit* is another LLR containing *Drosophila* secreted protein that functions in the development of the midline glial cells and the commissural axon tracts the cross the midline. This is presumably accomplished by cell adhesion events (Jacobs, JR, J. Neurobiol., 24(5):611-26, (1993)). Mammalian homologues of Drosophila *slit* have been shown to bind the heparan sulfate proteoglycan, glypican-1 (Liang, Y., Annan, RS., Carr, SA., Popp, S., Mevissen, M., olis, RK.,olis, RU, J. Biol, Chem. 18., 274(25):17885-92, (1999)). In general, heparan sulfate proteoglycans have been shown to ~~accummulate~~accumulate in Alzheimer's disease brains and specifically, glypican-1 is component of both senile plaques and neurofibrillary tangles (Verbeek, MM., Otte, Holler, I., van, den, Born, J., van, den, Heuvel, LP.,David, G., Wesseling, P., de, Waal, RM, Am. J. Pathol., 155(6):2115-25, (1999)). Heparan sulfate proteoglycans are also implicated in the regulation of cytokine signaling in B cells through the activation of CD40 (van, der, Voort, R., Taher, TE., Derksen, PW., Spaargaren, M.,van, der, Neut, R., Pals, ST, Adv, Cancer, Res.., 79:39-90, (2000))[[.]].--

Please amend the paragraph beginning on page 3, line 21, with the following amended paragraph:

--p37NB is a 37 kea LRR protein identified in human neuroblastoma cells (Kim, D. et al. (1996) Biochim. Biophys. Acta 1309: 183-188). Northern blot hybridization and RT-PCR studies show that p37NB is differentially expressed in several neuroblastoma cell lines. A related LRR

protein, PRELP, is characterized as a 42 kea secreted protein (Bengtsson, E. et al. (1995) J. Biol. Chem.. 270: 25639-25644). PRELP consists of 10 LRR motifs ranging in length from 20 to 26 residues with ~~asparigine~~asparagine at position 10. Northern analysis shows differential expression of PRELP in various tissues.--

Please amend the paragraph beginning on page 6, line 34 and continuing onto page 7 with the following amended paragraph:

-- The transcription factor NF-kB is sequestered in an inactive form in the cytoplasm as a complex with its inhibitor, IkB, the most prominent member of this class being IkBa. A number of factors are known to serve the role of stimulators of NF-kB activity, such as, for example, TNF. After TNF exposure, the inhibitor is phosphorylated and proteolytically removed, releasing NF-kB into the nucleus and allowing its transcriptional activity. Numerous genes are upregulated by this transcription factor, among them IkBa. The newly ~~synthesised~~synthesized IkBa protein inhibits NF-kB, effectively shutting down further transcriptional activation of its downstream effectors. However, as mentioned above, the IkBa protein may only inhibit NF-kB in the absence of IkBa stimuli, such as TNF stimulation, for example. Other agents that are known to stimulate NF-kB release, and thus NF-kB activity, are bacterial lipopolysaccharide, extracellular polypeptides, chemical agents, such as phorbol esters, which stimulate intracellular phosphokinases, inflammatory cytokines, IL-1, oxidative and fluid mechanical stresses, and Ionizing Radiation (Basu, S., Rosenzweig, K, R., Youmell, M., Price, B, D, Biochem, Biophys, Res, Commun., 247(1):79-83, (1998)). Therefore, as a general rule, the stronger the insulting stimulus, the stronger the resulting NF-kB activation, and the higher the level of IkBa transcription. As a consequence, measuring the level of IkBa RNA can be used as a marker for antiapoptotic events, and indirectly, for the onset and strength of pro-apoptotic events.--

Please amend the paragraph beginning on page 9, line 31 with the following amended paragraph:

-- The invention further relates to an isolated nucleic acid molecule of[[of]] SEQ ID NO:1, wherein the polynucleotide fragment comprises the entire nucleotide sequence of SEQ ID NO:1 or the cDNA sequence included in the deposited clone, which is hybridizable to SEQ ID NO:1.--

Please amend the paragraph beginning on page 10, line 22 with the following amended paragraph:

-- The invention further relates to the isolated polypeptide of [[of]]SEQ ID NO:2, wherein the full length protein comprises sequential amino acid deletions from either the C-terminus or the N-terminus.--

Please amend the paragraph beginning on page 11, line 5 with the following amended paragraph:

-- The invention further relates to a method of diagnosing a pathological condition or a susceptibility to a pathological condition in a subject comprising the steps of (a) determining the presence or amount of expression of the polypeptide of [[of]]SEQ ID NO:2 in a biological sample; and diagnosing a pathological condition or a susceptibility to a pathological condition based on the presence or amount of expression of the polypeptide.--

Please amend the paragraph beginning on page 22, line 12 with the following amended paragraph:

-- The polypeptide of this gene provided as SEQ ID NO:2 (Figures 1A-C), encoded by the polynucleotide sequence according to SEQ ID NO:1 (Figures 1A-C), and/or encoded by the polynucleotide contained within the deposited clone, HLRRSI1 (also ~~refered~~referred to as GPCR12#99, GPCR12#100, SILL1A and/or SILL1B), has significant homology at the nucleotide and amino acid level to a number of leucine-rich repeat containing proteins, which include, for example, the human caspase recruitment protein 7 protein (caspase_recruitment_protein; Genbank Accession No:gi|10198209; SEQ ID NO:3); the human nucleotide binding site protein protein (Nucleotide_Binding_site; Genbank Accession No:gi|10198207; SEQ ID NO:4); and the human cryopyrin protein (cryopyrin; Genbank Accession No:gi|17027237; SEQ ID NO:33). An alignment of the HLRRSI1 polypeptide with these proteins is provided in Figures 2A-C. --

Please amend the paragraph beginning on page 26, line 32 continuing onto page 27 with the following amended paragraph:

--Consistent with the strong homology to caspase ~~reseruitment~~recruitment proteins, antisense assays have shown the HLRRSI1 polypeptide to be involved in the regulation of mammalian NF-κB and apoptosis pathways. Subjecting A549 cells with an effective amount of a pool of five antisense

oligoncleotides (SEQ ID NO:34, 35, 36, 37, and 38) directed against the coding region of the HLRRSI polynucleotide resulted in a significant increase in IκBά expression/activity providing convincing evidence that HLRRSI at least regulates the activity and/or expression of IκBά either directly, or indirectly. Moreover, the results suggest that HLRRSI is involved in the negative regulation of NF-κB/IκBά activity and/or expression, either directly or indirectly. The IκBά assay used is described in Example 57 and was based upon the analysis of IκBά activity as a downstream marker for proliferative signal transduction events.--

Please amend the paragraph beginning on page 27, line 11 with the following amended paragraph:

-- The upregulation of IkBa due to the downregulation of HLRRSI1 places this leucine-rich repeat protein into a signalling pathway potentially involved in apoptotic events. This gives the opportunity to regulate downstream events via the activity of the protein HLRRSI1 with antisense polynucleotides, polypeptides or low molecular chemicals with the potential of achieving a therapeutic effect in cancer, autoimmune diseases. In addition to cancer and immunological disorders, NF-kB has significant roles in other diseases (Baldwin, A. S., J. Clin Invest. 107, :3-6 (2001)). NF-kB is a key factor in the pathophysiology of ischemia-reperfusion injury and heart failure (Valen, G., Yan. ZQ, Hansson, GK, J. Am. Coll. Cardiol. 38, 307-14 (2001)). Furthermore, NF-kB has been found to be activated in experimental renal disease (Guijarro C, Egido J., Kidney Int. 59, 415-425 (2001)). As HLRRSI1 is highly expressed in small intestine there is potential involvement of HLRRSI1 in treating ~~gastrointenstinal~~gastrointestinal diseases, particularly for cancers through the administration of HLRRSI1 and/or agonists thereof. --

Please amend the paragraph beginning on page 28, line 10 with the following amended paragraph:

-- In preferred embodiments, agonists directed against HLRRSI1 are useful for treating, diagnosing, and/or ameliorating autoimmune ~~diorders~~disorders, disorders related to hyper immune activity, hypercongenital conditions, birth defects, necrotic lesions, wounds, disorders related to aberrant signal transduction, immuno compromised conditions, HIV infection, proliferating disorders, and/or cancers.--

Please amend the paragraph beginning on page 28, line 29 continuing onto page 29 with the following amended paragraph:

--The strong homology to human leucine-rich repeat containing proteins, combined with the predominate localized expression in small intestine and its involvement in IkB modulation, suggests the HLRRSI1 polynucleotides and polypeptides may be useful in treating, diagnosing, prognosing, and/or preventing ~~gastrointesinal~~gastrointestinal diseases and/or disorders, which include, but are not limited to, ulcers, irritable bowel syndrome, diarrhea, polyps, absorption disorders, constipation, diverticulitis, vascular disease of the intestines, intestinal obstruction, intestinal infections, clcerative colitis, Crohn's Disease, hereditary hemochromatosis, gastroenteritis, mesenteric ischemia, mesenteric infarction, in addition to, metabolic diseases and/or disorders.--

Please amend the paragraph beginning on page 30, line 11 with the following amended paragraph:

--The HLRRSI1 polynucleotides and polypeptides, including agonists, antagonists, and/or fragments thereof, though preferably agonists of the present invention have uses which include, for example, modulating cellular proliferation. Likewise, the HLRRSI1 polynucleotides and polypeptides, including agonists, antagonists, and/or fragments thereof, though preferably ~~agonisits~~agonists of the present invention, may be useful for the treatment, detection, amelioration, and/or prevention of disorders related, or directly linked to, aberrant cellular proliferation, such as, for example, cancers.--

Please amend the paragraph beginning on page 31, line 23 with the following amended paragraph:

--As ~~deseussed~~discussed elsewhere herein, the Drosophia Toll proteins, including the human homologues thereof, have been implicated in modulating development and in non-infectious disease (Schuster, JM., Nelson, PS, J. Leukoc, Biol., 67(6):767-73, (2000)). --

Please amend the paragraph beginning on page 32, line 22 with the following amended paragraph:

--Moreover, the HLRRSI1 polypeptide shares significant ~~homolgy~~homology with caspase recruitment proteins. Aberrations of such proteins have been implicated in the incidence of a number of disorders related to aberrant apoptosis regulation, and in various inflammatory disorders

(Srinivasula, SM., Ahmad, M., Lin, JH., Poyet, JL., Fernandes, Alnemri, T.,Tsichlis, PN., Alnemri, ES, J. Biol, Chem. 18., 274(25):17946-54, (1999)).—

Please amend the paragraph beginning on page 4, line 34 and continuing onto page 5 with the following amended paragraph:

-- The transcription factor NF-kB is sequestered in an inactive form in the cytoplasm as a complex with its inhibitor, IkB, the most prominent member of this class being IkBa (Inhibitor of nuclear factor KappaB Alpha). A number of factors are known to serve the role of stimulators of NF-kB activity, such as, for example, TNF. After TNF exposure, the inhibitor is phosphorylated and proteolytically removed, releasing NF-kB into the nucleus and allowing its transcriptional activity. Numerous genes are upregulated by this transcription factor, among them IkBa. The newly synthezised IkBa protein inhibits NF-kB, effectively shutting down further transcriptional activation of its downstream effectors. However, as mentioned above, the IkBa protein may only inhibit NF-kB in the absence of IkBa stimuli, such as TNF stimulation, for example. Other agents that are known to stimulate NF-kB release, and thus NF-kB activity, are bacterial lipopolysaccharide, extracellular polypeptides, chemical agents, such as phorbol esters, which stimulate intracellular phosphokinases, inflammatory cytokines, IL-1, oxidative and fluid mechanical stresses, and Ionizing Radiation (Basu, S., Rosenzweig, K, R., Youmell, M., Price, B, D, Biochem, Biophys, Res, Commun., 247(1):79-83, (1998)). Therefore, as a general rule, the stronger the insulting stimulus, the stronger the resulting NF-kB activation, and the higher the level of IkBa transcription. As a consequence, measuring the level of IkBa RNA can be used as a marker for antiapoptotic events, and indirectly, for the onset and strength of pro-apoptotic events.--

AMENDMENTS TO THE SEQUENCE LISTING

In order to comply with the Notice to Comply With Requirements For Patent Applications Containing Nucleotide Sequence and/or Amino Acid Sequence Disclosures, the following has been amended within the originally submitted Sequence Listing, and is reflected in the Substitute Sequence Listing submitted concurrently herewith:

A) Lines <140> and <141> were amended to state the U.S. Serial Number and filing date of Non-Provisional Application U.S. 10/029,347;

B) New sequence SEQ ID NO:33 was added to the Sequence Listing to conform to 37 C.F.R. 1.821-1.825.

C) Original SEQ ID NOs:33 to 40 were reassigned to SEQ ID NOs:34 to 41.

D) New sequences SEQ ID NO:42, 43, and 44 were added to the Sequence Listing, along with the appropriate lines <221> thru <223>, to conform to 37 C.F.R. 1.821-1.825, and to address the Examiner's objection to Applicants failure to include the same.